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REMARKS

After entry of the present Amendment, claims 64-65, 70-72, 76-78, 80-83, 85-87, and 149-163 will be pending and under consideration. In the present communication, claims 73, 74, 75, 79, 84, 88-95, 97-106, and 111-148 have been canceled without prejudice or disclaimer, claims 64, 65, 70, 71, 72, 76-78, 80-83, and 149-151, 153, and 156 have been amended, and claims 157-163 have been added. A marked up version to show the changes made is attached herewith as Exhibit A. Entry of the amendments is respectfully requested, as well as reconsideration of the pending claims in view of the amendments and remarks herein.

Applicants and their representatives acknowledge with gratitude, Examiner Spector for granting them the interview of March 7, 2003.

The amendments submitted herewith are supported by the specification and original claims and do not add new matter. Amendments to claim 64 clarify that the sample is a nucleic acid sample from the skin. These amendments are supported for example, by claim 5 as originally filed which indicates that the sample can be a polynucleotide sample, and page 5, paragraph 24, which indicates that "polynucleotide," "nucleic acid," or "nucleic acid sequence" all refer to a polymer of deoxyribonucleotides or ribonucleotides. The amendment to claim 65 and newly added claim 161 are supported, for example, by page 3, lines 11-15, page 14, lines 10-14, and page 18, lines 1-7, and page 44, lines 10 to 14, which disclose removing the stratum corneum by tape stripping, and page 6, lines 23-29, which discuss the stratum corneum and the adhesiveness of the bottom of this layer. A skilled artisan would recognize based on these teachings, that upon removal of the stratum corneum by applying and removing an adhesive tape, cells associated with the stratum corneum will also be recovered. The amendment to claim 64, 70-72, 149, 150, and 156 reciting that the adhesive is an adhesive tape, are supported for example, by claim 4 as originally filed. The amendments to claims 76-78, 80-83, 151, and 153 recite the pending claim language as method steps, and therefore do not

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add new matter. Newly added claims 157 and 158 are supported for example, by page 7, lines 13-19, and page 13, lines 19-21. Claims 159-160 are supported for example, by page 2, line 10-11 and

Example 2. Claims 162 and 163 are supported for example, by page 3, lines 14 and 15.

get new inv.

"1 or more times.

*Doesn't disclose
as part of
process*

The Office Action indicates that newly introduced claim 156 has been renumbered as 149. However, claims 149 to 155 were added with the Supplemental Amendment filed July 22, 2002, which was received by the USPTO on July 29, 2002. Accordingly, Applicants' numbering of claims added in the Preliminary Amendment filed May 13, 2002, the Supplemental Amendment filed July 22, 2002, and the Supplemental Amendment filed October 1, 2002 are correct. If it would be helpful, the Applicants will provide a copy of the Supplemental Amendment filed July 22, 2002 upon request of the Examiner.

Formal Matter

Claim 65 and 115 stand objected to under 37 C.F.R. 1.75(c) as being of improper dependent form for allegedly failing to further limit the subject matter of a previous claim. Claim 65 allegedly fails to further limit claim 64, as allegedly any sample of skin would necessarily include one or more of the recited cell types. Claim 65 as amended recites that the skin sample comprises stratum corneum cells and cells associated with the stratum corneum which are removed by application and removal of the adhesive tape. Therefore, claim 65 further limits claim 64. Accordingly, Applicants respectfully request withdrawal of the objection of claim 65 under 37 C.F.R. 1.75(c).

Claim 115 is objected to in that it allegedly fails to further limit claim 104, because claim 104 allegedly states that the skin sample is obtained using an adhesive, and does not encompass scraping. Claim 115 is canceled herein. Accordingly, the rejection is moot, and Applicants respectfully request withdrawal of the rejection of claim 115 under 35 U.S.C. § 112, second paragraph.

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The use of the term "Scotch™ tape" is objected to in that allegedly there are innumerable tapes sold under the brand name of "Scotch," and therefore, the Office Action asserts that the term is not being used to indicate any single particular product. Accordingly, the Office Action alleges that the mere use of the term Scotch tape does not denote any particular product or property. The claims as amended do not recite "Scotch Tape." Accordingly, in view of the claim amendments, Applicants respectfully request withdrawal of the rejection of claims that included the term "Scotch Tape."

The Office Action alleges that the specification provides no information that would breath life and meaning into the term "non-invasive." Therefore, the Office Action identifies a meaning of the term from the Merriam-Webster website. The claims no longer recite the term "non-invasive." Accordingly, the meaning of the term "non-invasive" for the pending claims is irrelevant.

Double Patenting

Regarding the Divisional applications that are related to the pending application, the Office Action reminds Applicants to either cancel conflicting claims, or maintain a clear line of demarcation between the applications. The Applicants acknowledge the Examiner's comment and assert that no action is presently necessary.

Claim Rejection Under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 64, 73, 74, 76-83, 89-91, 94, 98-100, 102, 104-106, 111-135, and 137-149 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite, is respectfully traversed.

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Claims 64, 104, and 135 are allegedly indefinite in reciting that adhesive is applied "in a manner such that the skin nucleic acid profile after application is not affected for up to two hours." The claims no longer recite the above phrase cited in the rejection. Therefore, the rejection has been overcome. Accordingly, in view of the claim amendments, Applicants respectfully request withdrawal of the rejection of claims 64, 104, and 135 under 35 U.S.C. § 112, second paragraph.

The Office Action alleges that all claims that refer to tape are indefinite, as it is allegedly not clear what limitation is intended, since according to the Office Action, innumerable tapes are sold under the brand name Scotch™ Tape. The meaning of the term "tape" is well known. The Merriam-Webster website (<http://m-w.com/>) defines "tape" as "a narrow flexible strip or band," and defines "adhesive tape" as "tape coated on one side with an adhesive mixture; especially one used for covering wounds." The meaning of "adhesive tape" for the present invention is consistent with the well-known meaning of the term. Therefore, Applicants respectfully traverse the rejection with respect to the use of the term "adhesive tape."

Regarding the use of "Scotch™ Tape," as discussed above, the term is no longer recited in the claims. Therefore, the rejection with respect to this term has been overcome. Accordingly, in view of the claim amendments, Applicants respectfully request withdrawal of the rejection of claims 64, 104, and 105 under 35 U.S.C. § 112, second paragraph.

Claim 73 is allegedly indefinite because there allegedly is no antecedent basis for "the adhesive surface" of claim 64. Claim 73 is canceled herein. Accordingly, the rejection is moot, and Applicants respectfully request withdrawal of the rejection of claim 73 under 35 U.S.C. § 112, second paragraph.

Claims 76-84, 89-91, 98-100, 116-127, 135, and 137-148 are rejected in the Office Action as being indefinite because each of the claims allegedly recites a property of a nucleic acid, but allegedly

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does not further limit the claimed methods. The rejection is moot with respect to claims 79, 84, 89-91, 98-100, 116-127, 135, and 137 –148, because these claims are cancelled herein. With respect to the remaining rejected claims, the claims have been amended herein to be rewritten as methods steps. Therefore, the claim rejection have been overcome. As a result of these claim cancellations and amendments, Applicants respectfully request withdrawal of the rejection of claims 76-84, 89-91, 98-100, 116-127, 135, and 137-148 under 35 U.S.C. § 112, second paragraph.

Claim 94 stands rejected under 35 U.S.C. § 112, second paragraph as being indefinite as allegedly there is no antecedent basis for “the cellular material sample.” Claim 94 is cancelled herein, thereby rendering the rejection moot. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 94 under 35 U.S.C. § 112, second paragraph.

Claim 102 stands rejected under 35 U.S.C. § 112, second paragraph as being indefinite as allegedly there is no step in claim 95 that would generate a complementary equivalent to the isolated nucleic acid. Claim 102 is cancelled herein, thereby rendering the rejection moot. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 102 under 35 U.S.C. § 112, second paragraph.

Claim 104 stands rejected under 35 U.S.C. § 112, second paragraph as being indefinite as allegedly there is no method steps to a claim to a nucleic acid encoding a cytokine. Claim 104 is cancelled herein, thereby rendering the rejection moot. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 104 under 35 U.S.C. § 112, second paragraph.

Claim 135 stands rejected under 35 U.S.C. § 112, second paragraph as being indefinite as allegedly it is not clear what has been applied, or when. Claim 135 is cancelled herein, thereby rendering the rejection moot. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 135 under 35 U.S.C. § 112, second paragraph.

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Claim 149, stands rejected under 35 U.S.C. § 112, second paragraph as being indefinite for allegedly being self-referential. The claim as submitted was numbered as 156. However, the claim was renumbered by the Examiner, claim 149. As indicated above, claims 149 to 155 were added with the Supplemental Amendment filed July 22, 2002, which was received by the USPTO on July 29, 2002. Accordingly, the added claim was properly numbered as claim 156, and therefore is not self-referential. Accordingly, Applicants respectfully request that this claim number be changed back to 156, and request withdrawal of the rejection of claim 149 under 35 U.S.C. § 112, second paragraph.

Claim Rejection Under 35 U.S.C. § 112, First paragraph

Claims 64, 65, 70-84, 104-135, and 137-148 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way to reasonable convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Office Action indicates that the rejection is a new matter rejection. Applicants respectfully traverse the rejection.

The Office Action alleges that there is no basis in the specification for the recitation of claims 64, 104, and 135, that “in a manner such that the skin nucleic acid profile after application is not affected for up to about two hours.” The cited phrase is no longer recited in the pending claims as amended. Therefore, the rejection has been overcome. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 64, 104 and 135 under 35 U.S.C. § 112, first paragraph.

Claims 64-65, 70-72, 76-95, 98-106, 111-114, 116-148, stand rejected under 35 U.S.C. § 112, first paragraph, because allegedly the specification does not enable isolating stratum lucidum, stratum granulosum, stratum spinosum, or stratum basale cells using adhesive tape including a single application. The Office Action alleges that these innermost four layers would not be accessible

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enough to the tape with a limited number of applications. The claims as amended do not recite the layers cited in the Office Action. Accordingly, the rejection has been overcome. Therefore, Applicants respectfully request withdrawal of the rejection of claims 64-65, 70-72, 76-95, 98-106, 111-114, 116-148, under 35 U.S.C. § 112, first paragraph.

The Office Action alleges that enablement is not commensurate in scope with the claims with respect to isolating cells from the skin "in a manner such that the skin nucleic acid profile after application is not affected for up to about two hours." The Office Action cites Nickoloff et al., *Clin. Immunol. and Immunopath.*, 73: 63-68, as indicating that one would expect the cytokine profile of the skin to be altered by tape application. The amended claims do not include the phrase cited in the Office Action. Therefore, the rejection has been overcome. Accordingly, the Applicants respectfully request that the enablement rejection related to the phrase "in a manner such that the skin nucleic acid profile after application is not affected for up to about two hours" be withdrawn.

The Office Action alleges that enablement is not commensurate in scope with the claims with respect to using an adhesive that is not tape. The amended independent claims 64 and 149, from which the remaining claims depend, are directed at adhesive *tape*. Therefore, the rejection has been overcome. Accordingly, the Applicants respectfully request that the enablement rejection related to adhesives other than tape be withdrawn.

The Office Action alleges that the specification is not enabling with respect to DNA, because allegedly a person of ordinary skill would not accept that DNA levels would be indicative of cytokine expression. Applicants traverse the rejection. The Office Action alleges that the specification is not enabling of detection of DNA for diagnosis or distinguishing inflammatory reactions or any other disorder not directly associate with a change in the DNA itself. Furthermore, the Office Action argues that it is not clear that removal of a cell type that is nucleated will not affect cytokine production, meeting the limitation of claim 76.

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A method of the present invention according to independent claim 64, directed at a nucleic acid sample, or claim 76, directed at a DNA sample, does not require that the nucleic acid or DNA be indicative of cytokine expression, or that the nucleic acid or DNA must be used for distinguishing inflammatory reactions from another disorder. Therefore, for the pending claims it is irrelevant whether DNA levels are indicative of cytokine expression or inflammatory reactions. Furthermore, for pending claims directed at methods involving nucleic acids (i.e. claim 64 and dependents therefrom, except for claims 76 and 77) or DNA (i.e. claim 76), it is irrelevant whether isolation of a DNA sample affects cytokine production, because these claims do not recite a limitation related to cytokine production. Applicants have observed that DNA is isolated from skin samples using the tape stripping method of the present invention. Such DNA samples are useful, for example, for sample identification for forensic purposes. Accordingly, the Applicants respectfully assert that methods of the present invention that utilize a DNA sample are enabled by the specification as filed. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, regarding methods of the present invention directed at DNA samples.

The Office Action alleges with respect to claims 138, 141, and 146 that enablement is not commensurate in scope with the claims with respect to IL-2, IL-5, or IL-13 because it allegedly was not known as of the filing date of the present application that keratonocytes express these factors. Furthermore, it is alleged regarding leukotrienes and prostaglandins, that the specification is not commensurate in scope with these molecules because they are not encoded by nucleic acids. The rejection is moot because claims 138, 141, and 146 have been cancelled, without prejudice. Accordingly, the Applicants respectfully request that the enablement rejection related to IL-2, IL-5, IL-13, leukotrienes and prostaglandins be withdrawn.

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Claim Rejections Under 35 U.S.C. § 102

Claims 64, 65, 77-81,83, 85,86,89-91, 93, 95, 99-101, 103, 136, and 143 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Paludan et al., *J. Invest. Derm.* 99:830-835(1992). Applicants respectfully traverse the rejection. To anticipate an invention, each and every element of a claim must be found in a single prior art reference. MPEP § 2131; Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628,631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Paludan et al. disclose obtaining skin samples by scraping the epidermis with a scalpel. However, the pending claims recite that the sample is obtained by applying an adhesive to the skin and removing the adhesive from the skin. Paludan is silent as to obtaining a nucleic acid sample by applying and removing an adhesive to the skin. In fact, the Office Action acknowledges this fact in its 35 U.S.C. § 103 rejection (see below; and see Office Action at page 14, first paragraph). Therefore, Paludan et al. does not anticipate the present claim because it does not disclose all of recited elements of the pending claim. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 64, 65, 77-81,83, 85,86,89-91, 93, 95, 99-101, 103, 136, and 143 under 35 U.S.C. § 102(b)

Claim Rejections Under 35 U.S.C. § 103

The rejection of claim 136 as being anticipated by, or in the alternative as being obvious in view of Paludan et al. is respectfully traversed. Pending claim 136 is cancelled by the present Amendment. Therefore, the rejection of claim 136 under 35 U.S.C. § 103 is moot. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 136 under 35 U.S.C. § 103.

Claims 137, 139-140, 142, 144, 145, and 147 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Paludan et al. in view of Applicants admissions of the prior art. Pending

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claim 137, 139-140, 142, 144, 145, and 147 are cancelled by the present Amendment. Therefore, the rejection of these claims under 35 U.S.C. § 103 is moot. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 137, 139-140, 142, 144, 145, and 147 under 35 U.S.C. § 103.

Claims 70-74, 97, 104-114, and 129-131 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Paludan et al. in view of van der Molen et al. (*Arch. Dermatol. Res.* 289:514-518). Applicants respectfully traverse the rejection. To establish a *prima facie* case of obviousness there must be some suggestion or motivation in the prior art to make the claimed invention, there must be a reasonable expectation of success, and the prior art reference must teach or suggest all of the claim limitations. MPEP § 2142; *In re Vaeck*, 947 F.2d 488, 20 USPQ2d, 1438 (Fed. Cir. 1991). The reference teachings must be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification. *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). MPEP 2143.01.

The Office Action acknowledges that Paludan et al. do not teach or suggest taping to obtain a skin sample. However, the Office Action alleges that van der Molen et al. teach that “skin surface tape stripping with adhesive tape is a widely accepted and used method” for examining the localization and distribution of substances within the stratum corneum. Furthermore, the Office Action alleges that van der Molen et al. teach that cells from layers in addition to the stratum corneum can be obtained by taping. Finally, the Office Action alleges that it would have been obvious to modify the method of Paludan et al. using tape stripping instead of scraping, in view of van der Molen’s disclosure that cells from multiple layers may be so obtained, and in view of the desirability of the less invasive and less stressful tape stripping method.

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Applicants' invention is directed to a non-invasive method for obtaining a skin sample from which nucleic acid can be isolated or detected. The method includes applying and removing at least one application of an adhesive to the skin such that a skin sample adheres to the adhesive after its removal from the skin. As mentioned above and acknowledged in the Office Action, Paludan et al. disclose obtaining skin samples by scraping the epidermis with a scalpel, not by applying an adhesive to the skin and removing the adhesive from the skin, as recited in the pending claims. In fact, Paludan is silent as to obtaining a skin sample by applying and removing an adhesive. Therefore, Paludan et al. does not teach, suggest, or motivate this recited claim element.

The Office Action alleges that van der Molen provides this teaching. However, van der Molen pertains to compound penetration analysis, and does not teach using tape stripping to obtain nucleic acid samples of skin. Tape strips obtained in van der Molen were examined using X-ray microanalysis for the sole purpose of determining the distribution of skin over the tape surface in order to assess the efficacy of tape-stripping in removing skin from skin furrows for compound penetration studies. Van der Molen does not disclose or suggest using tape-stripping to obtain skin samples that can be used for isolation or detection of nucleic acids. In fact, Van der Molen teaches away from using tape stripping even in compound penetration studies in teaching that tape stripping is ineffective at uniformly removing stratum corneum cells across the entire skin because it does not remove cells from furrows (See for example, first paragraph of the Discussion section starting on the left column of page 517.). Accordingly, van der Molen emphasizes the difficulties in obtaining accurate results using tape stripping for compound penetration studies (See e.g., last paragraph of van der Molen, page 518, first full paragraph right column). Accordingly, van der Molen does not overcome the failure of Paludan et al. with respect to teaching using tape stripping to obtain a nucleic acid sample.

Furthermore, it is improper to combine van der Molen and Paludan et al. because one of ordinary skill in the art based on these references, would not have been motivated to combine them.

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First, these references relate to different technical areas. Paludan relates to amplifying mRNA from skin samples, while Van der Molen relates to using tape stripping for compound penetration studies. An ordinary artisan would not be motivated to combine teachings related to mRNA analysis studies with teachings related to compound penetration studies. Secondly, as mentioned above, van der Molen teaches away from using tape stripping, thereby teaching away from being combined with Paludan to isolate nucleic acid from the skin.

Finally, if the advantages of using the tape stripping method of the present invention over scraping, as acknowledged in the Office Action, for nucleic acid analysis would have been obvious based on Paludan et al. in view of van der Molen, then Paludan et al. would have used tape stripping to obtain their samples. As indicated in van der Molen, the use of repeated tape stripping in compound penetration studies dates back to at least 1986, well before the publication of Paludan et al. Therefore, if the advantages of tape stripping over scraping with respect to obtaining nucleic acid samples are obvious to an ordinary artisan, and if an ordinary artisan would combine teachings related to compound penetration studies with teachings related to RNA analysis, Paludan et al. would have used a tape stripping method to obtain samples for RNA analysis. However, Paludan et al. used an inferior scraping method, providing further evidence that the present invention which relates to using tape stripping in nucleic acid analysis studies is not obvious over Paludan et al. in view of van der Molen.

Accordingly, Applicants respectfully submit that neither Paludan et al. nor van der Molen et al., either separately or taken together, render the present invention obvious. Therefore, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claims 87, 88, and 98 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Paludan et al. in view of Frayne (U.S. Pat. No. 5,811,239) and claims 116, 119, 132, and 133 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Paludan et al. in view of van der Molen

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and further in view of Frayne (U.S. Pat. No. 5,811,239). The Applicants respectfully traverse the rejection. With respect to claims 88 and 98, canceled herein, the rejection is moot.

The Office Action acknowledges that Paludan et al. and van der Molen do not teach detection of DNA, the use of hybridization, or RNase protection assays. However, the Office Action alleges that Frayne teaches that it was well known in the art to detect DNA sequence variation for the purpose of identifying genetic disease, and allegedly teaches that PCR, hybridization, and RNase protection are well known techniques. The Office Action further alleges that a person of ordinary skill in the art would recognize that isolation of cells below the stratum corneum would yield cells with nuclei that could be analyzed by the allegedly routine methods taught in Frayne.

As mentioned above, Paludan et al. in view of van der Molen, do not teach, suggest or motivate the use of tape stripping in nucleic acid analysis studies, and therefore do not render obvious independent claims 64 and 149, from which claim 87 depends. Frayne, either alone or in combination with Paludan et al and van der Molen et al., does not overcome the failures of Paludan et al. and van der Molen et al. to teach using tape stripping to obtain a sample of skin for nucleic acid analysis. Frayne pertains to a method for detection of single base-pair DNA sequence variation in DNA samples. Frayne does not teach a tape stripping method. Accordingly, Frayne does not provide the missing teaching, suggestion, or motivation of Paludan et al. and van der Molen et al. with respect to using tape stripping to obtain a nucleic acid sample.

Claims 92, 94, 102, 128, and 134 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Paludan et al. (in the case of claims 128 and 134 in view of van der Molen), and further in view of Ramsey et al., U.S. Pat. No. 6,056,859 and Furcht et al. (U.S. Pat. No. 6,054,277). Claims 92, 94, 102, 128, and 134 are cancelled herein. Therefore, the rejection of these claims as unpatentable over Paludan et al. in view of Ramsey et al. is moot. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 92, 94, 102, 128, and 134 under 35 U.S.C. § 103(a).

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In the event any matters remain to be resolved in view of this communication, Examiner is requested to telephone Lisa A. Haile, J.D., Ph.D. at (858) 677-1456 so that a prompt disposition of this application can be achieved. Please apply any charges not covered, or any credits, to Deposit Account 50-1355.

Respectfully submitted,



Date: March 12, 2003

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Enclosures: Exhibits A and B



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EXHIBIT A:

CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

Please cancel claims 73, 74, 75, 79, 84, 88-95, 97-106, and 111-148.

Please amend the claims as follows:

64. (Thrice amended) A [non-invasive] method for obtaining [a skin] a nucleic acid sample from a [sample for use in isolating or detecting a nucleic acid in the] skin sample, the method comprising:

(a) applying [at least one application of] an adhesive tape to the skin and removing the adhesive tape from the skin [in a manner such that the skin nucleic acid profile after application is not affected for up to about two hours and] such that a sample comprising a nucleic acid adheres to the adhesive tape after its removal, [or, scraping the skin with an instrument to remove a sample comprising a nucleic acid from the skin], thereby obtaining a skin sample comprising a nucleic acid; and

(b) isolating or detecting the nucleic acid from the skin sample [of step (a)].

65. (Thrice amended) The method of claim 64, wherein the skin sample comprises [at least one of] stratum corneum cells[, stratum lucidum cells, stratum granulosum cells, stratum spinosum cells, and stratum basalis cells, or any combination thereof] and cells associated with the stratum corneum which are removed by application and removal of the adhesive tape.

70. (Thrice amended) The method of claim 64, wherein the skin sample is isolated by applying the adhesive [surface] tape to the skin between one and twenty five times to obtain the skin sample.

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71. (Thrice amended) The method of claim 64, wherein the skin sample is isolated by applying the adhesive [surface] tape to the skin between one and two times to obtain the skin sample.

72. (Thrice amended) The method of claim 64, wherein the sample is isolated by one application of an adhesive [surface] tape to an outer layer of the skin.

76. (Twice amended) The method of claim 64, wherein the isolating or detecting comprises isolating or detecting a nucleic acid that comprises a DNA.

77. (Twice amended) The method of claim 64, wherein the isolating or detecting comprises isolating or detecting a nucleic acid that comprises an RNA.

78. (Twice amended) The method of claim [77] 64, wherein the isolating or detecting comprises isolating or detecting an RNA that comprises an mRNA.

80. (Twice amended) The method of claim [79] 64, wherein the [polypeptide comprises] isolating or detecting comprises isolating or detecting a nucleic acid that encodes a cytokine.

81. (Twice amended) The method of claim [79] 64, wherein the [polypeptide comprises] isolating or detecting comprises isolating or detecting a nucleic acid that encodes an interleukin.

82. (Four-times amended) The method of claim [80] 64, wherein the [cytokine comprises] isolating or detecting comprises isolating or detecting a nucleic acid that encodes interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), interleukin-12 (IL-12),

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interleukin-13 (IL-13), granulocyte macrophage colony stimulating factor (GM-CSF), or an interferon, or any combination thereof.

83. (Twice amended) The method of claim 78, wherein the [polypeptide comprises] isolating or detecting comprises isolating or detecting a nucleic acid that encodes an inflammatory mediator.

149. (Twice amended) A [non-invasive] method for determining an expression profile in a skin sample, the method comprising:

- (a) applying at least one application of an adhesive tape to a sample site on the skin and removing the adhesive tape from the skin [in a manner such that the skin nucleic acid profile after application is not affected for up to about two hours, and] such that a sample comprising a ribonucleic acid (RNA) adheres to the adhesive tape after its removal, [or, scraping the skin with an instrument to remove a sample comprising RNA from the skin,] thereby obtaining a skin sample comprising RNA; and
- (b) isolating or detecting RNA from the skin sample of step (a) [for], thereby determining the expression profile in the skin sample.

150. (Twice amended) The method of claim 149, wherein the skin sample is isolated by applying the adhesive [surface] tape to the sample site of the skin between one and twenty five times to obtain the skin sample.

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151. (Twice amended)The method of claim 149, wherein [the RNA is] the adhesive tape is applied and removed such that the sample comprises mRNA.

153. (Twice amended)The method of claim 149, wherein [the RNA isolated or detected comprises] the adhesive tape is applied and removed such that the sample comprises RNA encoding a cytokine.

156. (Twice amended) The method of claim 149, wherein the skin sample is isolated by applying the adhesive [surface] tape to the sample site of the skin between one and two times to obtain the skin sample.